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C. W. Jameson, Ph. D.
NTP Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

This letter is in response to the announcement that the National Toxicology Program intends to review Alcoholic Beverages for possible listing in the Annual Report on Carcinogens, Ninth Edition.

My comments emanate from two perspectives; first, I have had for many years a personal, scientific interest in the subject of chemical carcinogenesis and especially in the possible interaction of alcohol in this process. My research in this area has indicated that alcohol is not a carcinogen and that in fact, under certain conditions it may even prevent the carcinogenic action of certain chemicals (e.g., Science 221:51, 1983; Drug Metabolism and Disposition 16:355, 1988). Secondly, because of my known, published statements on this subject, I have been asked by the alcoholic beverage industry to provide my views about the potential listing by the NTP of alcoholic beverages.

By way of introduction, I received my undergraduate degree in chemistry and my Doctor of Medicine degree from the University of North Carolina and have held professorships in departments of pharmacology and toxicology in medical schools at the Universities of North Carolina, Kentucky, and Louisville. I served as Professor and Chairman of the Department of Pharmacology and Toxicology at the University of Louisville School of Medicine from 1977 to 1997; currently I am Professor and Emeritus Chair. I have served on several editorial boards and am the author of over 100 peer reviewed articles on drug metabolism, pharmacokinetics, teratology, carcinogenesis and risk assessment.

The International Agency for Research on Cancer (IARC) has cited "Alcohol Drinking" as carcinogenic to humans and the State of California cites "Alcoholic beverages, when associated with alcohol abuse", to cause cancer; these are the only agencies of which I am aware that have listed alcoholic beverages as carcinogens. It is my understanding that the proposed listing by the

NTP of alcoholic beverages as a carcinogen will be based on the IARC monograph on alcohol. I was an observer of the working group at IARC in 1987 when the decision was made to assign "Alcohol Drinking" to 'Group 1, Carcinogenic to Humans' and am aware of the discussions that occurred among the working group during those deliberations. Although the final vote on the classification was a majority of the working group, it was by no means unanimous. I should like to cite briefly some of the problems encountered in classifying alcohol as a carcinogen.

The first problem is that although numerous experiments have been done in a variety of animal species on the possible carcinogenicity of alcohol, no such experiment in animals has yet demonstrated that alcohol is a carcinogen, with the exception of a single experiment that was not adequately performed. The IARC report confirms and so states this conclusion in its final evaluation. Consequently, the evaluation was done entirely on reports of epidemiological studies.

As you are aware, epidemiological studies must be interpreted with considerable caution because of possible bias, confounding and chance. In general, causality is inferred only after the Hill criteria of strength of the association, specificity, consistency and dose-response have been satisfied. These criteria are, of course, cited in the preamble of the IARC document for evaluating the epidemiological studies. The large number of these studies on alcohol drinking and the incidence of cancer provided a basis for evaluation; they revealed that for many of the anatomical sites the associations were weak and inconsistent. Some studies showed an increase, some no association, and some a decrease. Of course, in evaluating by anatomical site, the attempt is being made to find specificity, i.e., a specific site.

After much deliberation, it was concluded by a majority of the working group that there was sufficient evidence for a causal association at five sites: the oral cavity, pharynx, larynx, esophagus, and liver. For each of these sites, however, the studies are inconsistent and there are important confounders that still exist. In the opinion of a number of scientists these inconsistencies and confounders completely invalidate the inference of causality. A copy of a letter to the editor of the British Journal of Cancer by several colleagues and me is attached that details the inconsistencies and confounders that exist for each of these sites. Please consult that letter for a more complete explanation.

In brief, many of the studies were confounded by concurrent cigarette smoking and when only nonsmokers were evaluated the associations disappeared or actually showed a decrease. Also, it is of particular interest that in most of the studies by Tuyns, drinkers of 40 grams of alcohol per day are combined with nondrinkers for the comparison groups; he explains this technique as necessary because in France where most of his studies were done there are almost no

nondrinkers. It should be remembered that Health and Human Services considers 40 grams of alcohol to be about three drinks (one drink = 14 grams).

The studies by Tuyns of the esophagus are particularly interesting because the groups were large and the nondrinker groups can actually be evaluated against the drinker groups. The drinkers of less than 40 grams per day showed a decreased risk of esophageal cancer compared to the nondrinker group.

In the reports on liver cancer, many had no data on hepatitis B serology; furthermore, hepatitis C was unknown at that time. Each of these viruses has been strongly associated with liver cancer in the absence of alcohol consumption.

Since publication of the IARC monograph, studies have continued to appear on the possible association of alcohol and cancer. Although I have followed this literature with interest, there still has not been a definitive publication, or series of publications, that have come to my attention that would allow an inference of causation. A review of all of these publications is beyond the scope of this letter, but not beyond the range of consideration of the NTP for its listing.

The articles on alcohol and cancer that have appeared in the decade since publication of the IARC monograph also fail to satisfy the Hill criteria. They have been inconsistent, with some showing an association, some showing no association, and some showing an inverse association. Furthermore, none of the associations are strong and a dose response is not apparent. Many confounders have been identified, including cigarette smoking, viral infections, diet, education, menopausal status, etc. The studies suffer from these limitations and consequently do not provide a conclusion of causality. To implicate alcohol as a carcinogen without adequate evidence that it is a causal agent will have wide impact in eroding our scientific credibility because of the significant public interest in these beverages. Just as important, it will divert our efforts from the identification of the actual causative agents for cancer in our lifestyles.

In summary, after years of closely following the subject, I do not find that there is any convincing evidence that alcohol is a carcinogen. In my opinion, it would be an error in scientific judgment to list alcoholic beverages as carcinogens. There are many other issues to consider relative to alcohol drinking, both pro, such as beneficial effects on cardiovascular disease, and con, such as drinking and driving; however, these issues should not emerge in the objective decision regarding evaluation of its potential carcinogenicity. Those issues should be dealt with in another arena.

Thank you for the opportunity to convey my observations to the NTP process for evaluation in consideration of the listing of alcoholic beverages as carcinogens. I should be most grateful for the opportunity to provide more information, either in writing or in person, to the appropriate NTP evaluating bodies.

Sincerely,

William J. Waddell, M.D.
Professor and Emeritus Chair

Enclosure

LETTER TO THE EDITOR

Alcohol and cancer

Sir – The source of information cited in the Guest Editorial by A.J. Tuyns (*Br. J. Cancer*, 1991, 64, 415–416) does not support the points made about the dose-response relationship between alcohol consumption and cancer. Some of us participated in the IARC Working Group preparing the monograph on Alcohol Drinking and witnessed the very controversial discussions over the conclusions; further, we are all on record as disagreeing with IARC's qualitative conclusions about alcohol. We disagree with Tuyns on some of his interpretations and particularly his extrapolations of the data.

The Preamble specifically states (page 27 of the Alcohol Drinking monograph) that the Evaluations 'refer only to the strength of the evidence that these agents are carcinogenic and not to the extent of this carcinogenic activity (potency) nor to the mechanism involved.' Participants in the IARC Working Group are specificaliy instructed that dose must not be considered in the evaluation; if it is carcinogenic at *any* dose, then it is to be classified as a carcinogen. Tuyns' Editorial does not reflect this constraint and even proceeds to proclaim that 'there is a continuous risk curve – comparable – to curves observed in laboratory animals exposed to many other carcinogens.' The data support neither Tuyns' statements nor his mathematical expressions of the additive effect with tobacco and nutrition.

Tuyns correctly states that repeated attempts to produce cancer in experimental animals by administration of ethanol have failed; this is also the conclusion in the IARC monograph on Alcohol Drinking. In fact, it was one reason that the decision was made to title the monograph 'Alcohol Drinking' and not 'Alcohol'; nevertheless, Tuyns, in his guest editorial, neglects this distinction and even misquotes the IARC document to state that 'alcohol is carcinogenic to man.'

The inability to demonstrate that ethanol is carcinogenic in experimental animals requires that the evaluation be done exclusively from epidemiological studies. The IARC cohort and case-control studies, in the aggregate, found no convincing association with alcohol drinking for cancer of the stomach, colon, pancreas, breast or lung. The data at these sites showed either no correlation or a mixture of negative and positive correlations. Data at other sites showed either no association or was so sparse that an evaluation was precluded. From these epidemiological studies the IARC monograph concludes that the occurrence of malignant tumors in only five sites, i.e., 'oral cavity, pharynx, larynx, esophagus and liver is causally related to the consumption of alcoholic beverages.' As Tuyns correctly points out, most of these studies are confounded by concurrent cigarette smoking. Although IARC contends that the association exists even after adjustment for tobacco smoking, accurately adjusting for cigarette smoking in the absence of sufficient independent data on each factor alone is problematic at best. Therefore, it is instructive and indeed enlightening to examine the epidemiological studies on nonsmokers for these five sites.

For the oral cavity and pharynx, the IARC document cites four reports in nonsmokers. In two of these (Wynder *et al.*, 1957; Tuyns *et al.*, 1988) there was no increase in cancer in drinkers over the incidence in controls. In another study (Rothman & Keller, 1972 or Rothman, 1976) a trend for an increase with drinking was not significant by the Cochran-Mantel-Armitage test. In the last study (Elwood *et al.*, 1984), the increase in cancer was statistically significant only at the highest level of alcohol intake, but the incidence of cancer in the lowest level of alcohol intake was lower than that expected from the controls. Elwood *et al.* also found a significantly increased risk with low socio-economic status, the unmarried state and poor dental care. It is interesting that in Tuyns' own report, the group with the lowest level of drinking also had fewer cases than expected from their controls. However, Tuyns combines nondrinkers with drinkers consuming up to 40 grams per day of alcohol into a single group; consequently, it is difficult to analyse his data.

Laryngeal cancer is of special interest because it is a site which does not have direct contact with ingested alcohol. The IARC document cites four reports of studies in nonsmokers. The data in the Wynder *et al.* (1976) report show no cases of laryngeal cancer among nonsmoking drinkers whereas there were five cases among nonsmoking nondrinkers. Burch *et al.* (1981) show a calculated estimate of an increase in risk of laryngeal cancer in nonsmoking drinkers with increasing consumption of alcohol; however, they provide no data for nonsmoking drinkers and the degree of validity of their calculated adjustments from smokers is unknown. The other two studies (Elwood *et al.*, 1984; Tuyns *et al.*, 1988) have already been discussed above in the paragraph on the oral cavity and pharynx. The data of Elwood *et al.* were, in fact, combined for oral cavity, pharynx and larynx. Tuyns *et al.* calculated an expected 9.4 cases of cancer of the endolarynx for their 0–40 grams/day group; however, only seven cases were observed.

The literature on cancer of the esophagus is perhaps the most interesting. Tuyns (1983) is the only study cited by IARC on esophageal cancer in nonsmoking drinkers, and it is the largest study (743 esophageal cancer patients) of any of the five sites in nonsmokers. Tuyns makes his relative risk (RR) calculations in this report, as in all his reports of which we are aware, by combining the nondrinkers with drinkers of up to 40 grams per day into his control 'nondrinker' group. His justification apparently is that there are so few truly nondrinkers in the populations he has studied. However, in this report he does give raw data for nondrinkers and groups of drinkers in increasing increments of 20 grams per day from which calculations can be made. Several interesting observations emerge from these calculations. Light to moderate drinking males (up to 40 grams per day) showed empirically a decreased risk of esophageal cancer (0–20 grams/day, RR = 0.48; 20–40 grams/day, RR = 0.35). This possible protective effect is not only obscured by combining these drinkers with nondrinkers, but it also makes his apparent RR greater for heavier drinkers. The only group which is significantly different from true nondrinkers is drinkers of more than 120 grams/day. If all levels of drinking are combined, the RR is not significantly elevated above that for nondrinkers. If one argues that the number of cases in the nondrinkers is so small so as to invalidate the calculation, one may examine his data for females where the number of nondrinkers is greater. The RR in females at all levels of drinking combined is not elevated above that for nondrinkers yet the nondrinker comparison group is larger than his combined so-called 'nondrinker' group of males. In addition, the RR's calculated for each group of female drinkers show the same decreased risk in light to moderate drinkers.

The effect of dietary factors on cancer of the oral cavity, pharynx and esophagus has been studied in several reports (e.g. Tuyns *et al.*, 1987; Graham *et al.*, 1990; Gridley *et al.*, 1990). Foods and nutrients have been identified which significantly increase or decrease the risk for cancer at these sites. Among the protective substances were fresh meat, polyunsaturated fats, carotene, fruits and vegetables; whereas nitrite-containing meats, increased calories and fat were

associated with an increased risk. Since the nutritional status of heavy drinkers could very well reflect a dietary pattern that would increase their risk to cancer at these sites, one cannot conclude that alcohol is a carcinogen at these sites. As Tuyns *et al.* (1987) state so well: 'high colinearity – limits the possibility of using statistical procedures for controlling for multiple confounding items; it also indicates how dangerous it may be to draw conclusions based on crude analyses.'

The decreased risk of esophageal cancer for nonsmoking drinkers of less than 40 grams/day which may be calculated from Tuyns' data can be noted in other reports which are cited in the IARC document. In fact, when dose-response data are present in reports so that one can evaluate the shape of the dose-response curve against nondrinkers, a 'J'-shaped dose-response curve commonly appears. Articles continue to appear which support this observation. For example, Boffeta and Garfinkel (1990) found decreased mortality from all cancers for light drinkers in a very large study of US men.

Interpretation of a possible association between liver cancer and alcohol drinking poses problems in confounding in addition to cigarette smoking because of the known carcinogenicity of some prevalent hepatitis viruses and because of the frequency of metastatic liver cancer. Indeed, most of the studies cited in the IARC document were noted by the Working Group to have no data on hepatitis B virus serology. In fact, in the largest study (Trichopoulos *et al.*, 1987) where most of the cases were histologically confirmed and data on hepatitis B carrier status and cigarette smoking were available, no association with ethanol consumption was found after adjustment for the other factors. Furthermore, hepatitis C virus was unknown at the time the IARC document was prepared, and it is also strongly associated with hepatocellular carcinoma (Hasan *et al.*, 1990; Bruix *et al.*, 1989). Infection with hepatitis C virus also correlates with heavy alcohol consumption (Yasuyama, 1991; Mendenhall *et al.*, 1991).

In summary, we do not think that the weight of the evidence indicates that alcohol is a carcinogen at all. The animal studies, despite their deficiencies in design, support this view since a carcinogen potent enough to induce tumours in five target sites in one species would, by current experience, be expected to produce tumours in other species as well even with limited or intermittent periods of administration. If, indeed, there is a correlation between alcohol drinking and cancer at a few sites, the shape of the dose-response curve is most likely a 'J' shape similar to that found frequently for alcohol drinking and cardiovascular disease. If there is a correlation between heavy alcohol consumption and cancer at some sites, there is nothing to indicate that it is a causal association; the cause could just as likely be a confounding covariable such as tobacco smoking, diet, poor dental care, socio-economic status or viral infection.

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